EVIDENCE ON DEVELOPMENTAL AND REPRODUCTIVE TOXICITY OF PERCHLORATE

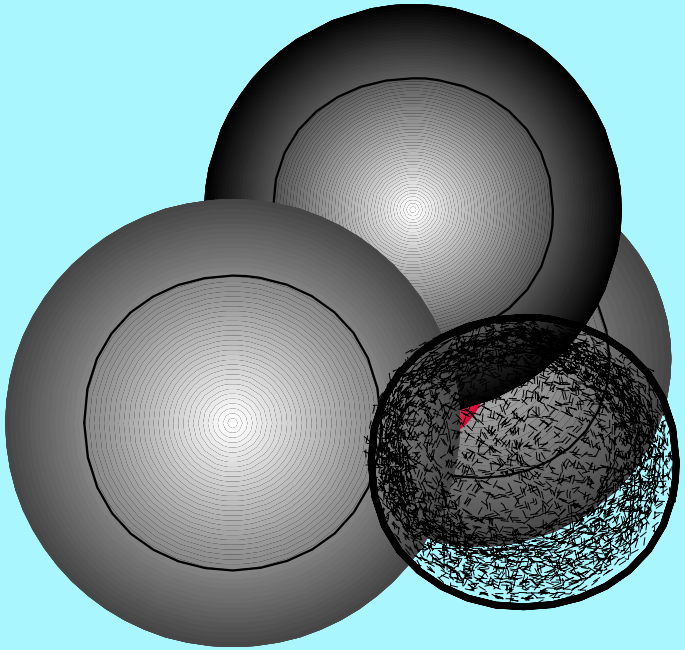
REPRODUCTIVE AND CANCER HAZARD ASSESSMENT SECTION

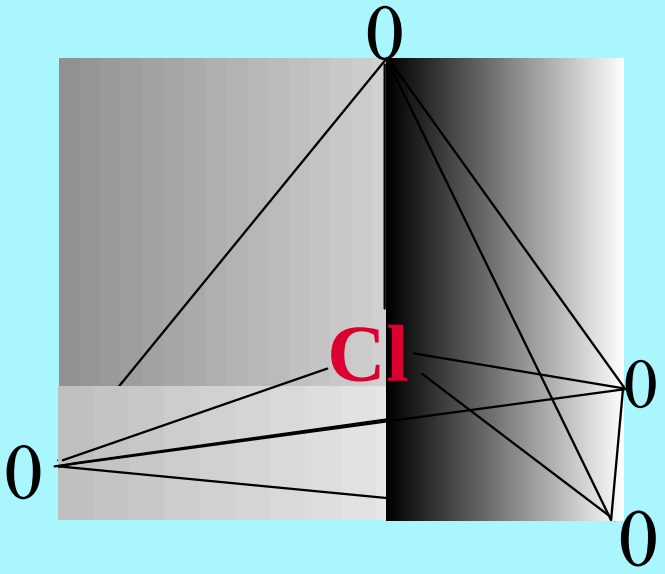
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

AUGUST 11, 2005

PERCHLORATE

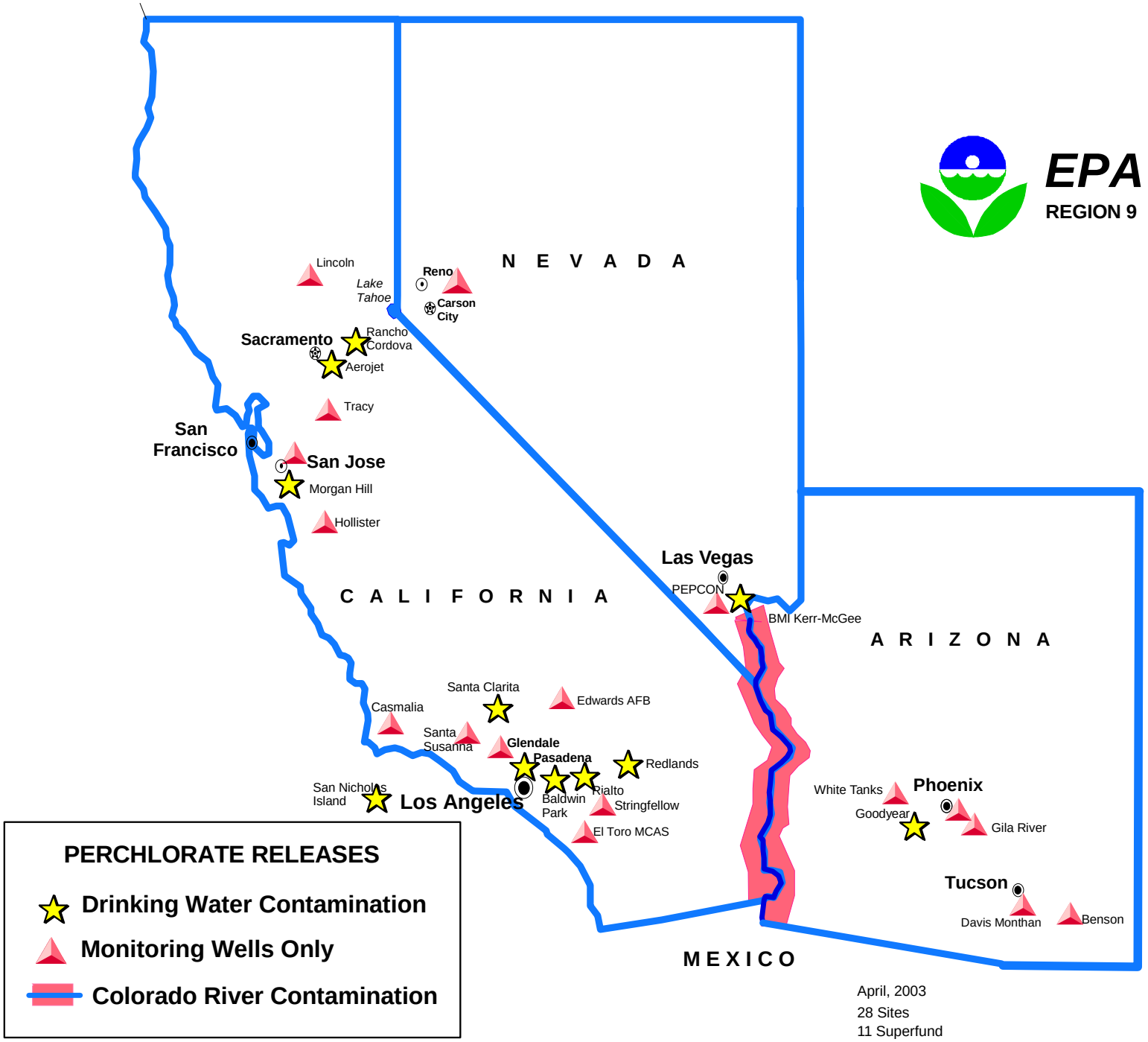
ClO_4^-





Perchlorate Chemistry

- Oxidizing agent, high-energy compound
- Soluble anion, stable in groundwater
- Component of rocket fuel, flares, fireworks, explosives
- Was used to treat hyperthyroidism
- Competitive inhibitor of iodide
- Low-level, natural sources exist
- Accumulates like other salts in some plants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White Tanks
Phoenix
Goodyear
Gila River
Tucson
Davis Monthan
Benson
PERCHLORATE RELEASES
Drinking Water Contamination
Monitoring Wells Only
Colorado River Contamination
April, 2003
28 Sites
11 Superfund

Issues for Hazard Identification

- Occurrence of an adverse effect
- Potential for the occurrence of an adverse effect based on data from animal models and available information on physiology and pharmacology in humans
- Sensitive populations
- Uncertainties/reasons for concern

Hazard Identification Materials Presented to the DART Identification Committee (DART IC)

1. **Public Health Goal for Perchlorate (OEHHA, 2004) and**
2. **Assessment of the National Research Council of the National Academies of Science titled *Health Implications of Perchlorate Ingestion (*NRC, 2005).**
3. **Some of the original studies and links to additional materials that are electronically available and may aid in the review**
4. **Greer et al., 2002, Environ Health Perspect. (110) 9; 927-937**.
5. **Baldridge et al., (2004) in Reprod Toxicol., 19(2):155-161**.

Hazard Identification Materials Presented to the DART IC

Greer et al., 2002, Environ Health Perspect. (110) 9; 927-937.

- based on human trials of the effects of perchlorate exposure on iodine uptake by the thyroid,
- used by OEHHA as the basis for the PHG and
- by the National Academy of Sciences (NAS) as the basis for estimating the Reference Dose (RfD) for perchlorate.

Hazard Identification Materials Presented to the DART IC

- **Baldridge et al., (2004) in Reprod Toxicol., 19(2):155-161**.
- evaluated the female reproductive system in rodents
- was published after the last meeting of the NAS committee and
- was not reviewed in the reports of OEHHA and the NAS

Developmental and Reproductive Toxicity Issues from Perchlorate Exposure

- Inhibits iodine uptake into thyroid
- Altered thyroid function, decreased growth and cell metabolism
- Potentially can cause goiter in pregnant women and developmental effects including decreased IQ in offspring
- Reduction of the amount of nutritional iodide available to the developing neonate during lactation

Hypothyroidism, Iodine Deficiency, Pregnancy and Neurological Deficits in Offspring

• Link between hypothyroidism caused by iodine deficiency during pregnancy and mental retardation in the offspring is well established

•Mild and probably asymptomatic hypothyroidism in pregnant women can adversely affect their children's subsequent performance on neuropsychological tests

(Haddow et al., NEJM., 1999)

Overview of Studies on the Effects of Perchlorate

- Multiple low-dose effects in rat studies

  Conducted at Argus Laboratories sponsored by the Perchlorate Study Group (PSG)

  – Changes in rat brain development

  – Behavioral changes

  – Immunological effects

- Human effects also considered for weight-of-evidence

Outline of Animal Studies and Findings

- NOAEL pup = 0.1 mg/kg-day (thyroid morphometry and histopathology)
- Mating and fertility parameters unaffected at doses up to 30 mg/kg-day, but it can affect the thyroid.
- ↑TSH and ↓T(3) and T(4) levels at 0.1 mg/kg-day and above (considered adaptive and not adverse).
- Brain histopathology: ↑thickness of the corpus callosum at 10 mg/kg-day group pups on DL 12.
- No behavioral effects at doses up to 10 mg/kg-day (passive avoidance, swimming watermaze, motor activity, and auditory startle).

Tests were screening measures - unlikely to detect subtle alterations

Conclusions on the developmental and reproductive toxicity of perchlorate from PHG and NAS findings

Conclusions from PHG findings

"Four sensitive subpopulations are identified in this evaluation:

(i) pregnant women and their fetuses, especially those who are getting less than a sufficient amount of iodine;

(ii) lactating women, especially those who are getting less than a sufficient amount of iodine,

(iii) infants; and

(iv) individuals with thyroid problems."

- PHG (page 1)

Critical endpoint chosen by OEHHA for PHG

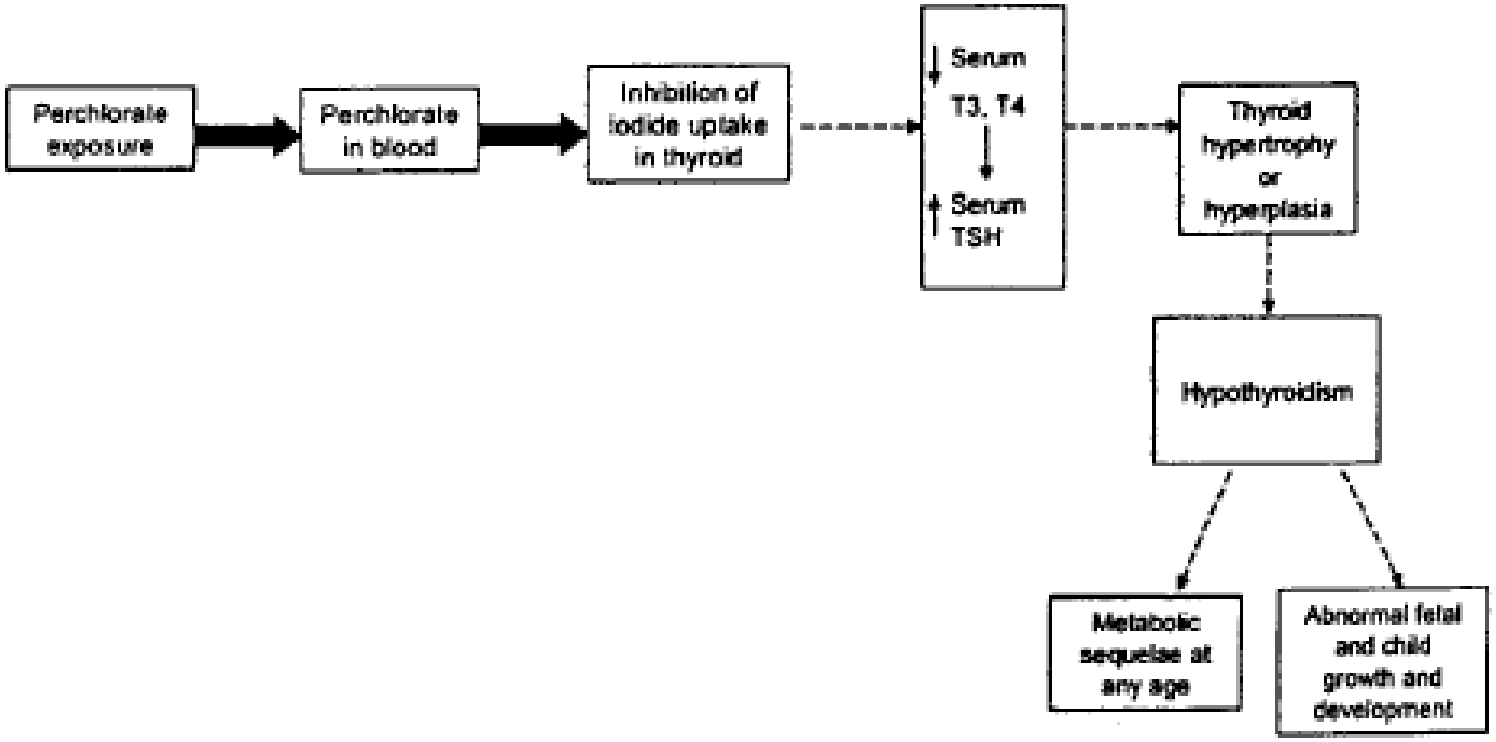
- Inhibition of thyroid iodide uptake
  - The first event in the chain of anti-thyroid effects of perchlorate
  - Reversible inhibition of sodium iodide symporter (NIS)
  - Treated as an undesirable effect, as it is a precursor to developmental effects in fetus

Conclusions from NAS findings

- "Fetuses and preterm newborns constitute the most sensitive populations, although infants and developing children are also considered sensitive populations."

  - NAS 2005 (page 27)

Mode-of-Action Model of perchlorate toxicity in humans (NAS., 2005)



Animal Toxicology Studies

- "…although studies in rats provide useful **qualitative** information on potential adverse effects of perchlorate exposure they are limited in their utility for **quantitatively** assessing human health risk associated with perchlorate exposure." (NAS., page 10)

- "…inhibition of iodide uptake is the only effect that has been consistently documented in humans exposed to perchlorate."
- "Given the mode-of-action model…. the committee does not agree that transient changes in serum thyroid hormone or TSH concentrations are adverse health effects; they are simply biochemical changes that might precede adverse effects."
- The No Observable Effect Level (NOEL) value from this study (Greer et al., 2002), is a health-protective and conservative point of departure for use in the RfD

- (NAS document: pages 13-15)

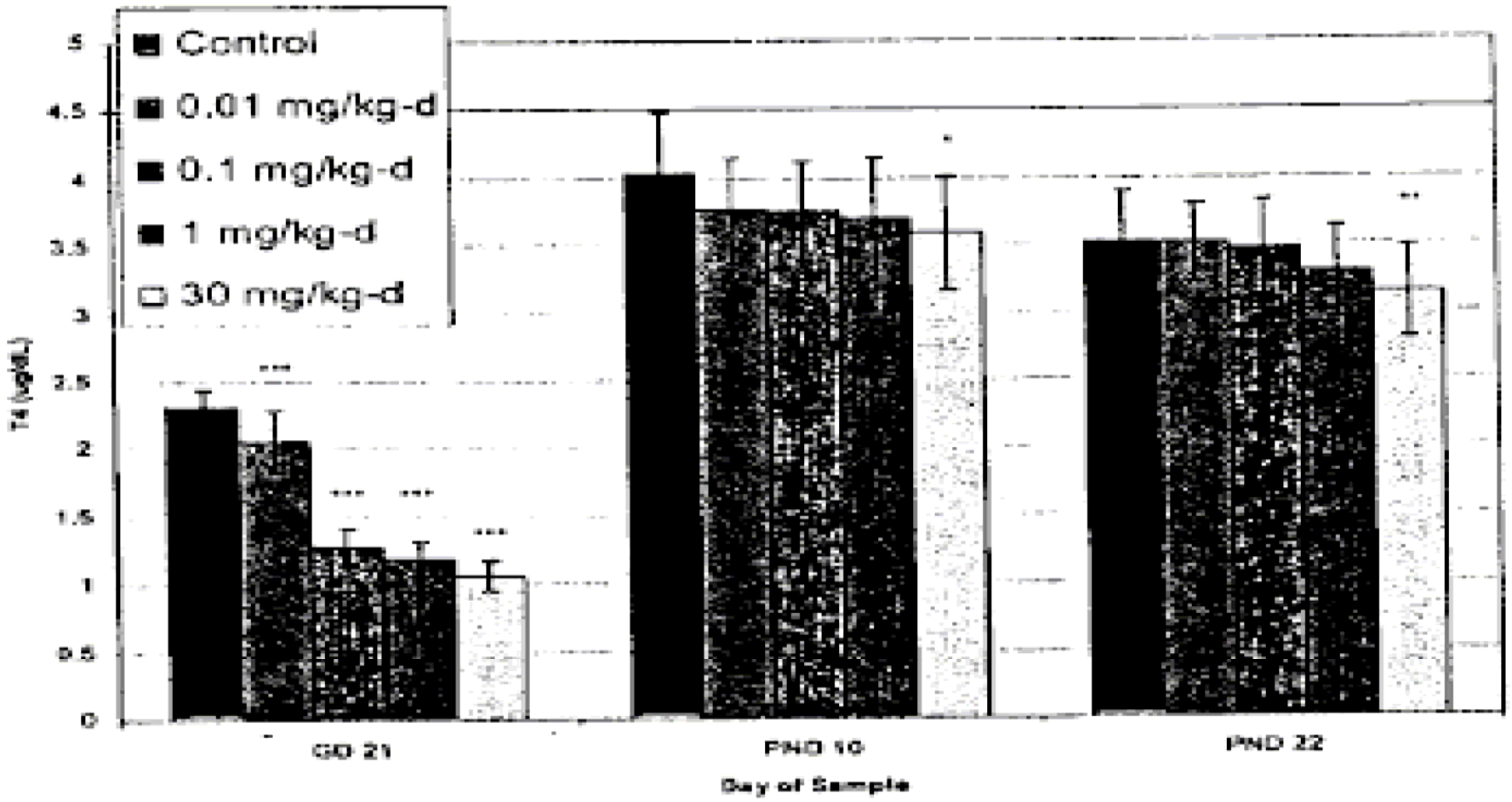
Perchlorate effects in fetus – Issues

- Impacts of iodide uptake inhibition
  - maternal thyroid, placenta, fetal thyroid (when present)
- Perchlorate crosses placenta, but kinetics of fetal uptake/elimination not clear
- Brain and other organs developing rapidly, prior to formation of fetal thyroid. At this stage embryo/fetus is dependent on maternal thyroid output.
- No reserves of thyroid hormones in fetus

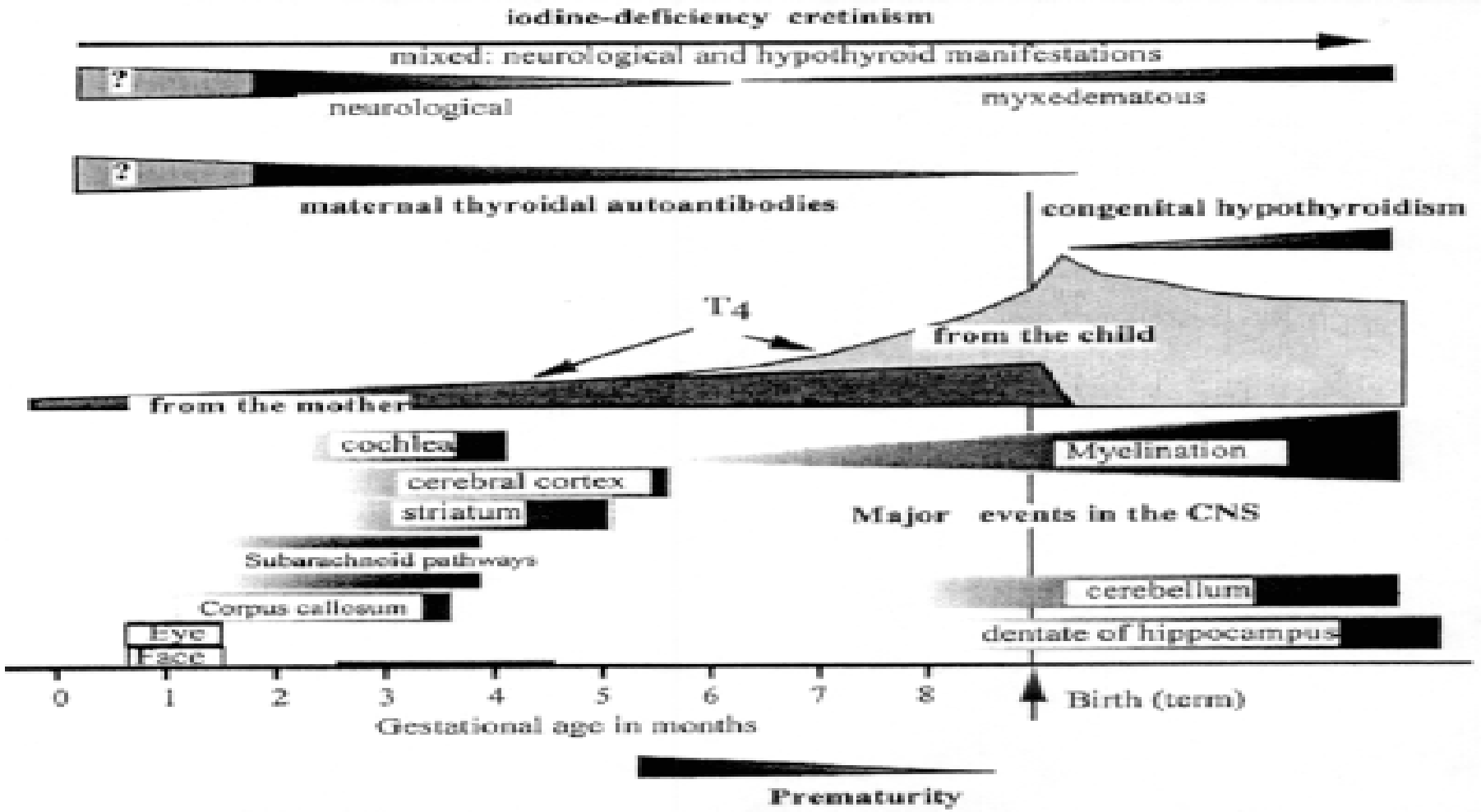
Specific effects on developing nervous system

- Decline in free thyroxine (free T4) with normal thyrotropin (TSH) levels between **5/6 weeks and 24 weeks** post conception (in humans) may affect cortical neuron migration and organization of the neocortex and hippocampus - (Auso et al., 2004 Endocrinology 145 (9): 4037-4047)
- Effects at specific critical timepoints can be irreversible if T4 treatment were delayed - (Pop et al., 2003 Clinical Endocrinol., 59: 282-288)

Thyroid Hormone Profile in Dams from Animal Studies (Argus Labs., 2001)



Approximate timing of major insults to the brain from hypothyroxinemia, superimposed on major events of neurodevelopment



Effects of low thyroid hormone in the developing brain

- Defects in migration of cortical neurons, possible disrupted cortical lamina (1st trimester)
- Decreased rate of neuronal proliferation in cerebellum (2nd trimester)
- Delayed assembly of microtubules
- Delayed development of neurotransmitter receptors and neural activity (3rd trimester)
- Delayed myelin deposition (post-natal)

Maternal influences on fetal susceptibility

- Pregnant women in U.S. suffering from subclinical hypothyroidism
- Women with low iodide excretion – surrogate for iodine intake (NHANES III)

Concerns for fetal susceptibility to perchlorate

- Known critical periods in brain development, with irreversible effects
- Rat brain morphological and behavioral effects at low perchlorate doses
- Well-documented mental retardation from both maternal and infant thyroid insufficiency
- Mental/behavioral effects in infants and children from perchlorate exposures in utero and/or post natally not yet examined

Tellez et al., 2005

Effects of perchlorate during early pregnancy -thyroid hormones and effects in newborns

- Pregnant women and their offspring in an area with high perchlorate in water (114 µg/L)
- Only neonatal parameters examined
- Perchlorate levels appear to be more than that can be accounted for from drinking water
- Urinary Iodine levels were ~325 µg/L (higher than median values for the U.S - NHANES III.)
- Women examined at 16 ± 4.1 weeks of pregnancy not earlier; FT4 levels measured as early as 15.3 weeks of pregnancy were not lowered and were comparable across all three groups.

Perchlorate effects on the reproductive system - Issues

- Rapid excretion of perchlorate ($t_{1/2}$ ~8 hrs)
- Several month's supply of thyroid hormones in thyroid of iodine-sufficient healthy adults
- Brain and other organs already developed in adult, not sensitive to short-term effects
- Effects on Reproductive system

Female Reproductive system (Baldridge et al., 2004: GD7-21)

Perchlorate (mg/kg/day)	# Dams	# Female Pups	Findings
0.4	6	24	↓ # Antral.Follicle (>100Kμm^2)
0.4 + T4	6	24	↓ # Antral.Follicle (>100Kμm^2)
0.4	6	24	Atresia, ↓ total number of follicles & maturation ↓ # Preantral & Antral Follicle(50->100μm^2)
0.4 +T4	6	24	↓ # only Antral Follicle (50->100μm^2)
Control (saline)	7	28	
Control (T4-treated)	7	28	

Female reproductive system

Baldridge et al., 2004

- Ammonium perchlorate (AP) reduced the number of preantral and antral follicles in certain size classes in female pups of rats exposed during a critical period of development (GD 7-21).
- T4 attenuated the effects of AP on small preantral and antral follicles, but not on medium or large antral follicles.

Male Reproductive System

- Currently no studies that have specifically evaluated the effects of perchlorate on the male reproductive system
- Two-generation studies in laboratory animals found no effects on fertility; effects on sperm density and spermatid density were noted but were not statistically significant.
- Effects from exposure of laboratory animals to other chemicals that cause thyroid hormone perturbations (e.g. PTU) indicate that the target site is the **sertoli cell** and effects observed include **sertoli cell proliferation** resulting in **macroorchidism** and **alterations of sertoli cell differentiation**

Male Reproductive System

- Siglin et al. (2000) or Springborn Lab (1998): PHG, p21; NAS, p149

  Animals: Adult SD rats

  Doses: 0, 0.01, 0.05, 0.2, 1.0, or 10 mg/kg-d for 14 or 90 days

  Endpoints: testis weight; histopathology

- Thuett et al. (2001): PHG, p28

  Animals: Deer mice

  Doses: 0, 0.001, 1.0, 1000 µM in drinking water, gestation & lactation
  Endpoints: testis weight in male pups on PND 21

- York et al. (2001) or Argus Res Lab (1999): PHG, p25; NAS, p150

  Animals: SD rats

  Doses: 0, 0.3, 3.0, 30 mg/kg-d, two-generation repro study.

  Endpoints:

  Parent: fertility, testis weight, histopathology.

  F1 males: fertility, testis weight; sperm parameters, histopathology.

Perchlorate Scientific Issues for Prop 65

- The Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65, California Health and Safety Code 25249.5 *et seq*.) specifies that "a chemical is known to the state to cause cancer or reproductive toxicity…if in the opinion of the state's qualified experts **the chemical has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer or reproductive toxicity**."

Hazard Identification and Prop 65

- The DART IC reviews the data to determine whether or not the chemical being considered is a hazard.
- The issue of the dose or exposure level at which the chemical is a hazard is considered later, at the time of determining the Safe Harbor Number, i.e., Maximum Allowable Dose Level (MADL) for the chemical.